REMARKS

I. Status of Claims

Claims 1-8, 10-18, and 21-72 are pending in the instant case. Claim 29 stands rejected under 35 U.S.C.§102 (a) and (b), and claims 1-6, 10-18, and 21-72 stand rejected under 35 U.S.C.§103. Claims 78 has been objected to for depending from a rejected base claim, but has otherwise been deemed allowable.

II. The Rejection of Claim 29 under 35 U.S.C.§102 should be withdrawn

The examiner rejected claim 29 under 35 U.S.C.§102(b) as being anticipated by Alitalo, et al. W/O 97/05250 (hereinafter referred to as "Alitalo"), and under 35 U.S.C.§102(a) as being anticipated by Achen, et al. W/O 98/07832 (hereinafter referred to as "Achen.") Alitalo and Achen disclose the polynucleotides that encodes two novel growth factors, VEGF-C and VEGF-D, respectively, both ligands for the tyrosine kinase receptor VEGFR-3.

Claim 29 recites a kit for use in the treatment of restenosis. Specifically, claim 29 recites a container holding VEGF-C and/or VEGF-D polynucleotide operatively linked to a promoter for the promotion of expression of VEGF-C and/or VEGF-D in blood cells, and a label that describes the use of the VEGF-C and/or VEGF-D agent for the inhibition of restenosis of a blood vessel. The examiner seems to concede that the two cited references fail to disclose the label recited in Claim 29. In rejecting claim 29, the examiner asserted that the "labels and instructions do not contribute any essential patentable feature to the invention." The applicants respectfully traverse.

The Patent Office's reviewing court has previously held that functional labeling can contribute a patentable feature to an invention so as to distinguish it from prior art. In *In re Miller*, 164 U.S.P.Q. 46, 418 F.2d 1396 (C.C.P.A. 1969), the inventor appealed a Patent Office rejection of claims directed to a measuring cup with volumetric indica that are half their actual volume that is indicated. The purpose of the invention in *In re Miller* was to allow the cook to prepare half of the volume of any given recipe without having to mentally calculate the volume needed for half of each ingredient. The Patent Office had rejected the claims as obvious over a simple measuring cup, alleging that printed matter failed to contribute a patentable feature to a recited structure. The Court reversed the rejection, stating that "printed matter, in

an article of manufacture claim, *can* be given 'patentable weight.'" *Id.* at 49. The important patentability inquiry to the court was whether there was "a new and unobvious functional relationship between" the article of manufacture and the printed material that formed the combination recited in the claim. *Id.*

The reasoning of the Court in *In re Miller* shows that the rejection of claim 29 is based on a false premise that labels or instruction cannot impart patentable weight. The proper inquiry is whether the label in combination with the VEGF-C or VEGF-D material together provide a "new and unobvious functional relationship." With respect to the cited references, the answer is affirmative, because neither reference discloses the treatment of restenosis.

The functional relationship between the various elements of claim 29 becomes clear upon a brief review of the critical role that labeling plays in the therapeutic arts. The United States Food and Drug Administration places severe restrictions on the form that a therapeutic must be take to be used on human beings. See, Code of Federal Regulations, Title 21, Volume 8. In particular, Code of Federal Regulations, Title 21, Volume 8, Part 610.60-610.65 (Exhibit A), provides an inventor with six labeling requirements that are specific to biological products such as VEGF-C and VEGF-D. Here, the label element is not only a requirement for use as a therapeutic, but it contributes to defining a new and unobvious function to make the VEGF-C/D polynucloetide useful in the treatment of restenosis. The label element imparts a patentable feature to claim 29 by contributing a new and unobvious function or use.

Furthermore, *In re Miller* expresses the notion of functionality that the courts have recently addressed in the context of software and business method patents. In the software context, the courts have reasoned that software is patentable when the software (essentially printed matter recorded on a media) directs a machine to perform "a useful, concrete and tangible result." *State St. Bank & Trust Co. v. Signature Fin. Group*, 47 U.S.P.Q.2d 1596, 1601 (Fed. Cir. 1998). In the same way that software functionally directs a machine to perform a useful result, the label of claim 29 converts the VGEF-C/D kit into a useful tool for the treatment of restenosis. In accordance with Judge Rich's reasoning in *In re Miller,* and by analogy to the treatment of software patents, the rejection of claim 29 should be withdrawn.

III. The Rejection of Claims 1-6, 10-18, 22-32, 49-69, and 71, 72; and, 21-51, 57-69, and 71, 72 under 35 U.S.C.§103(a) should be withdrawn

Claims 1-6, 10-18, 22-32, 49-58, 63-69, 71 and 72 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Isner (U.S. Patent No. 5,652,225 (the '225 patent), and U.S. Patent No. 5,830,879 (the '879 patent)) in view of Alitalo. Claims 21-51, 57-69, 71 and 72 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Isner (the '225 and '879 patent) in view of Achen *et al.* (WO 98/07832).

The '225 patent purports to disclose a method for the delivery of a nucleic acid to an arterial cell comprising contacting the cell with a hydrophilic polymer incorporating the nucleic acid (See Abstract, Column 2, Line 25-27 of the '255 patent.) A central purpose of the '225 patent is the use of a "hydrophilic polymer incorporating the nucleic acid, thus avoiding the use of a double-balloon or porous balloon catheter..." (Column 2, Line 1-4.) Thus, the '225 patent is directed to a particular mode of delivering a nucleic acid such as VEGF to avoid using a more complicated, less effective procedure.

The '879 patent purports to teach a method for treatment of blood vessels that have been injured in a variety of circumstances. The treatment involves the inducement of reendothelization of the lining of the injured blood vessel with the use of vascular endothelial growth factor (VEGF). The method involves the selecting a human host having an injured blood vessel, administering to the injured blood vessel DNA encoded with the VEGF gene, and the expression of the VEGF gene to induce reendothelization.

As the examiner has acknowledged, the '225 and '879 patents do not mention the use of VEGF-C or VEGF-D nucleic acids or those proteins.

The examiner cites the Alitalo reference as allegedly teaching that VEGF-C may be an inducer of angiogenesis of blood and lymphatic vessels, and in the formation of collated vessels around critical stenoses and into injured tissues after infection. Achen *et al.* is cited by the examiner as allegedly teaching that VEGF-D stimulates endothelial cell proliferation and angiogenesis.

The examiner alleges that it would have been obvious to one of skill in the art to substitute VEGF-C for VEGF in the methods described in the '225 and '879

patents because of an alleged equivalence in function between VEGF-C and VEGF: "Therefore, it was known at the time of filing of the instant application that VEGF-C had the same function as the VEGF of Inser in the stimulation of blood vessel formation, and therefore for the inhibition of stenosis or restenosis and therefore a suitable alternative to VEGF." See, Page 5, Line 1-4 of October 25, 2001 Office Action. Similarly, with respect to VEGF-D the examiner alleged as follows: "Therefore, because VEGF-D stimulates angiogenesis and it was known at the time as taught by Isner that any VEGF will function to inhibit restenosis, it would have been obvious at the time the invention was filed to include VEGF-D in limitations of the claims and a possible alternative to VEGF." See, Page 5-6 of October 25, 2001 Office Action. The applicants respectfully traverse.

Contrary to what the examiner asserted in the Office Action, the art did not suggest that VEGF-C or VEGF-D were functional equivalents of VEGF or provide a reasonable expectation of success if one were to substitute these molecules for VEGF in any particular method. In fact, the art taught that VEGF-C and VEGF have significantly different structures and perform different functions in a biological system.

There are significant difference in the sequence of VEGF and both VEGF-C and VEGF-D. Achen, *Proc. Natl. Acad. Sci. USA*, 95, 548-553 (1998), disclosed that the amino acid sequence of VEGF-C and VEGF-D share only a 30 and 31 percent sequence homology with VEGF, respectively. People skilled in the art at the time of the present invention did not consider a 30 percent sequence similarity to be a reliable predictor similarity in function. For example, the Transforming Growth Factor (TGF) superfamily of proteins posses widely divergent activities even though members of the TGF-superfamily share anywhere from 25-50 percent amino acid similarity. *See,* Kingsley, *Genes & Development*, 8, 133-146; Massague, *Annu. Rev. Cell. Biol.*, 6, 597-641 (1990). Epidermal Growth Factor (EGF) and Fibrillin illustrate the significant unpredictability in the function of proteins that share a low level of sequence similarity. EGF and Fibrillin share a 22 percent sequence similarity, but EGF functions to stimulate the proliferation and differentiation of many cell types and Fibrillin is a structural protein in microfibrils. *See,* Bell, *et al.*, *Nucl. Acids Res.*, 14(21), 8427-8446 (1986); Corson, *et al.*, *Genomics*, 17, 476-484 (1993). Further,

both VEGF-C and VEGF-D genes encode long N- and C-terminal pro-polypeptides at the point where the VEGF sequence ends. These differences in the sequence, structure and function of VEGF-C/D as compared to VEGF lead Achen *et al.* to conclude that VEGF-C and VEGF-D define a distinct 'subfamily' of VEGF related proteins. *See.* Achen, *et al.*, *Proc. Natl. Acad. Sci. USA*, 95, 548-553 (1998). One skilled in the art would not have been motivated to substitute either molecule for VEGF in a therapeutic method with a reasonable expectation of success.

In terms of function, the art thought that VEGF-C and VEGF-D have their greatest affinity for the Flt4 (VEGFR-3) receptor, and do not exhibit binding for VEGFR-1. In contrast, VEGF has greater affinity for VEGFR-2, and binds VEGFR-1, but exhibits no significant affinity for VEGFR-3. People skilled in the art would not have expected molecules with different receptor binding profiles to behave identically *in vivo* or be readily substitutable in therapeutic methods with an expectation of success. In this regard, it is worth observing that VEGFR-3 expression becomes largely restricted to *lymphatic* endothelia in mature mammals. The Alitalo reference cited by the examiner reports that when VEGF-C was expressed under the control of a keratin promoter in transgenic mice, the mice displayed abundant growth of lymphatic vessels under the skin (where the promoter would have been most active). (See Alitalo at Example 29, pages 88-91.) In contrast, the prior art relating to VEGF and VEGFR-2 largely focuses on their effects on blood vessels. This evidence of divergent function at both the molecular and systemic level provides compelling evidence that the art would not have considered VEGF-C/D to be suitable replacements for VEGF with any reasonable expectation of success. In fact, the motivation to make the substitution at all is unclear. In consideration of these significant differences between VEGF and VEGF-C/D it seems counter-intuitive to suggest that it would be obvious to substitute VEGF-C/D for VEGF in a treatment for restenosis.

In the particular field of the treatment of restenosis, there also uncertainty about the actual utility of VEGF as an agent. Isner & Asahara, International Patent Publication No. WO 98/19712, suggests treating injured blood vessels and accelerating reendothelialization following angioplasty by isolating a patient's endothelial progenitor cells and re-administering such cells to the patient. The authors

suggests, however, that the effectiveness of using an angiogenesis-promoting growth factor, such as vascular endothelial growth factor (VEGF), may be limited by the lack of endothelial cells on which the VEGF will exert its effect. *See,* Isner & Asahara, page 11, line 18-23. Without a clear teaching of the utility of using VEGF as an agent in the treatment of restenosis, it seems that one skilled in the art would posses little motivation to substitute VEGF-C/D for VEGF, very different proteins in structure and function.

DeYoung & Dichek, *Circ. Res., 82*: 306-313 (1998) state that VEGF gene delivery does not currently appear destined for application to human coronary restenosis, and that two independent studies suggest that VEGF delivery may actually worsen arterial intimal hyperplasia. Thus, one skilled in the art would not have a reasonable expectation of success in, or a motivation to substitute VEGF-C/D for VEGF.

Based upon the significant differences in the structure, sequence and function between VEGF-C/D and VEGF, there was neither the motivation to substitute VEGF-C/D for VEGF as a treatment for restenosis, nor a reasonable expectation that such a substitution would lead to a successful treatment for restenosis. Therefore, we respectfully request that the rejection of claims 1-6, 10-18, 22-32, 49-58, 63-69, 71 and 72; and 21-51, 57-69, 71, and 72 under 35 U.S.C.§103(a), over Isner (the '225 and '879 patents), in view of Alitalo or Achen, be withdrawn.

IV. The Rejection of Claims 21-51, 57-69, 71, and 72 under 35 U.S.C.§103(a) should be withdrawn

Claims 1-6, 10-18, and 22-72 stand rejected by the examiner under 35 U.S.C. 103(a) as being unpatentable over either Isner in view of Alitalo (as applied to claims 1-6 and 10-18), or Isner in view of Achen (as applied to claims 21, and 33-48) and further in view of Martin et al.

As discussed above, the Isner reference cited by the examiner involves two separate disclosures, the '225 and the '879 patents. The '225 patent discloses a new method for the delivery of material to an injured blood vessel without the use of a double balloon catheter and the '879 patent discloses an method of repairing an injured blood vessel with the use of VEGF. Alitalo and Achen both disclose the DNA

sequences and thus the protein sequences for the VEGF-C and VEGF-D proteins, respectively. The examiner cites Martin et al. for suggesting the use of a particular delivery device.

This rejection is primarily based upon the same logic as are the other rejections discussed above, namely, that it would have been obvious to on of skill in the art to substitute either VEGF-C or VEGF-D for VEGF in the existing VEGF art and to use the device of Martin. However, as outlined above, the examiners assertion of the obviousness of the substitution of VEGF-C or VEGF-D for VEGF breaks down in light of the significant differences in the structure and function between VEGF and both VEGF-C and VEGF-D. Thus, there is neither the reasonable expectation of success in the substitution of VEGF-C/D for VEGF, nor the motivation to treat VEGF-C/D as equivalents to VEGF, and consequently the use of VEGF-C/D as agents in treating restenosis cannot be considered obvious in light of the cited art.

Therefore, we respectfully request that the examiners rejection of claims 1-6, 10-18, and 22-72 under 35 U.S.C. 103(a) as being unpatentable over either Isner in view of Alitalo (as applied to claims 1-6 and 10-18), or Isner in view of Achen (as applied to claims 21, and 33-48) and further in view of Martin et al., be withdrawn.

V. Conclusion

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By: 

David A. Gass
Reg. No. 38,153

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